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Applicant GEORGIADES, Jerzy, A.	

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(57) Abstract

A dietary supplement comprises a combination of colostrinin and at least one of lactoferrin and selenium.

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DIETARY SUPPLEMENT

The present invention relates to a dietary supplement and, in particular, to a dietary supplement for promoting the functioning of the immune system. The invention also relates to baby formulas.

When a baby is born, its immune system is normally dormant and non-functioning but, as the baby grows, the immune system becomes active. There has recently been a hypothesis that mother's colostrum contains components which contribute to the awakening and development of the immune system. One particular such component is called colostrinin. It is found, inter alia, in ovine and human colostrum.

As a result of our studies, we have found that the administration of colostrinin to an infant may be of singular importance to the full development of the immune system, and that it is possible that an infant fed solely on bottle formula milk preparations may, as a result of not receiving colostrinin, have a poorly developed immune system. An imperfectly developed immune system can lead to the development of serious diseases such as atopic allergies including, for example, as asthma and skin allergies. There have even been reports that a reduced function of the immune system can lead to senility in old age and, possibly, to Alzheimer's disease.

It is impractical to solve this problem by trying to take steps to ensure that all infants are breast fed, because some mothers are physically unable to breastfeed, and others may not be able to breastfeed because they are undergoing treatment themselves and are taking drugs which should not be passed on to the baby through breast milk. Also, in some areas of the world, there is a social stigma attached to breastfeeding.

We have now devised a dietary supplement formula for promoting the correct functioning of the immune system. The supplement can be given to non-breast fed infants, for example by inclusion in their baby formulas or powdered milk feed. It can also be given to breast-fed infants, and to children and adults at any time of their life, especially if they show signs of immune deficiency. Thus, the invention provides a way of treating an individual with a view to promoting their immune system whether or not

they have been breast-fed, and whatever their state of health.

The dietary supplement of the present invention comprises colostrinin in combination with at least lactoferrin. We have found that this combination of substances exhibits synergism.

By "dietary supplement" we mean a preparation or formulation which is added to or otherwise included in a person's normal diet, and is present in addition to the normal diet. Thus, for example, a dietary supplement of the invention can be:

(a) in the form of a liquid or solid, eg. powder or as individual dosage units such as baby food formula, tablets or the like to be added to food or drinks, or taken with them;

(b) added to a foodstuff during its preparation, such as added to powdered milk feed for babies or otherwise included in children's and adults' foodstuffs.

By "dietary supplement" we do not intend to embrace foodstuffs per se that may naturally contain the components of the supplement according to the invention.

The synergism can be further enhanced by the addition of selenium to the composition.

The lactoferrin, selenium and colostrinin present in the preferred food supplement of the invention can each be of natural or synthetic origin, eg. produced by recombinant DNA technology. The supplements will normally also include a physiologically acceptable diluent or carrier such as is appropriate to the particular use intended.

In a preferred embodiment, the selenium is in the form of a physiologically acceptable selenoprotein, such as selenocysteine. The selenium can be provided in the form of glutathione peroxidase. The selenium can be provided in the form a complex in which it is bound to Lactobacillus acidophilus or yeast protein. Furthermore, the selenium protein complex is preferably human and may be from a recombinant or natural source. Selenium is known to be a weak inducer of the cytokines and in particular of gamma interferon. It is particularly preferred that the selenium be present in the dietary supplement in the form of selenium rich proteins rather than as a salt, since when administered as for example selenium picollinate, it is generally not fully utilised by the body.

The term "colostrinin", as used herein refers to a complex of polypeptides which, in its natural form, is obtained from any mammalian colostrum. Colostrum is the thick, yellowish fluid produced by a mammalian mother's breasts during the first few days after childbirth. It is the first lacteal secretion post parturition and it contains a high concentration of immunoglobulins (IgG, IgM and IgA) and nonspecific proteins. It is replaced by mature breast milk about four to five days after birth. Compared with mature breast milk, colostrum contains low sugar and iron. However, colostrum is richer in lipids, proteins, mineral salts, vitamins and immunoglobulins. It also contains various floating cells such as granular and stromal cells, neutrophils, monocyte/macrophages and lymphocytes and includes growth factors, hormones and cytokines.

Various factors have been isolated and characterised from mammalian colostrum. In 1974, Janusz et al (FEBS Lett., 49, 276-279) isolated a proline-rich polypeptide (PRP) from ovine colostrum. It has since been discovered that mammals other than sheep have analogues of PRP as a component of their colostrum. PRP has since been called colostrinin (and is sometimes called colostrinine).

M. Janusz & J. Lisowski in "Proline-Rich Polypeptide (PRP) - an Immunomodulatory Peptide from Ovine Colostrum" (Archivum Immunologiae et Therapiae Experimentalis, 1993, 41, 275-279) mentioned that PRP from ovine colostrum has immunotropic activity in mice.

A. Dubowska-Inglot et al in "Colostrinine: a proline-rich polypeptide from ovine colostrum is a modest cytokine inducer in human leukocytes" (Archivum Immunologiae et Therapiae Experimentalis, 1996, 44, 215-224) discussed the use of colostrinin in the treatment of Alzheimer's disease. The use of colostrinin in the treatment of Alzheimer's disease, and other conditions, was also discussed in WO-A-98/14473.

Colostrinin, in its natural form, is obtained from mammalian colostrum. As described in WO-A-98/14473, analysis by electrophoresis and chromatography has shown that colostrinin has the following properties:

(i) it has a molecular weight in the range 16,000 to 26,000 Daltons (this was shown by electrophoresis in the presence of SDS);

(ii) it is a dimer or trimer of sub-units each sub-unit having a

molecular weight in the range 5,000 to 10,000 Daltons (this was shown by acrylamide gel electrophoresis in the presence of SDS);

(iii) it contains proline, and the amount of proline is greater than the amount of any other single amino acid (this can be shown by conventional amino acid analysis).

It has also been shown that colostrinin and the sub-units making up the colostrinin are non-polar.

By means of these techniques it was shown that ovine colostrinin has a molecular weight of about 18,000 Daltons, is made up of three non-covalently linked sub-units each having a molecular weight of about 6,000 Daltons and includes about 22 wt% proline. The amino-acid composition of ovine colostrinin was shown to be made up of the following number of residues per sub-unit: lysine - 2, histidine - 1, arginine - 0, aspartic acid - 2, threonine - 4, serine - 3, glutamic acid - 6, proline - 11, glycine - 2, alanine - 0, valine - 5, methionine - 2, isoleucine - 2, leucine - 6, tyrosine - 1, phenylalanine - 3 and cysteine - 0.

The colostrinin used in the food supplement of the invention may be derived naturally from any mammalian source, such as humans, bovine, goats or sheep. Alternatively, the colostrinin may be made synthetically, for example, by recombinant DNA techniques. The colostrinin need not necessarily be in a pure form but may instead be, for example, partially purified as, for example, I_gG-colostrinin complex, or in a crude preparation form like whey, so long as the form is physiologically acceptable.

The source of the lactoferrin is also not critical but it should preferably be of bovine, ovine or human origin (or derived therefrom). Most preferably, human lactoferrin and/or human recombinant lactoferrin is used.

The preferred amounts of each ingredient per unit dose of the dietary supplement is as follows: colostrinin from about 12½ micrograms to about 200 micrograms; lactoferrin from about 10 micrograms to about 100 milligrams; and selenium, in the form of seleno-cysteine, from about 2.5 to about 100 micrograms. However, for young babies the preferred amount is below 2.5 micrograms, for example 0 to 1.0 micrograms.

The preferred dosage of the dietary supplement of the invention is one preferred

unit dose per day.

The dietary supplement of the invention may further include other biologically active substances such as the cytokines present in colostrum other than colostrinin, and hormones. For example, the supplement may include a natural cytokine preparation containing members of the interferon family (including interferon α and interferon γ), interleukin 1-α, interleukin 1-3, interleukin-6, 8, 10, 12, 16, tissue necrosis factor α, G-CSF (granulocyte colony stimulating factor), M-CSF (macrophage CSF), TGFα (transforming growth factor) and TGFβ.

The physiologically acceptable carrier of the dietary supplement of the present invention is chosen to be suitable for the intended use. Examples of suitable carriers include for example a solution of the hydrolysates of β casein in the form of 6.000 m.w. peptides, phosphate buffered saline (PBS), and whey.

The most preferred route for administering a dietary supplement of the invention is oral, especially in a form in which the supplement is maintained in contact with the oral and/or pharyngeal and/or intestinal tract mucosa. One preferred form is that of a baby food formula. Another preferred form is that of a lozenge, designed to be dissolved in the mouth. In the lozenge or other form, the dietary supplement may further include various flavouring or sweetening agents such as sucrose, mannose, lactose, maltose, trehalose, cold water soluble starch or other such ingredients known in the art.

As will be understood, the food supplement of the invention can be in a number of other forms such as powders, tablets, or liquid drinks and baby formulas. When in powder form, they can be added to a foodstuff such as, for example, a powdered milk formulation (or cheese or yoghourt or indeed any other foodstuff). The source of the milk is not important and may, for example, be cow, goat or sheep. The powdered milk formulation may be made up with a liquid to form a drink.

In another form, the dietary supplements of the invention can be included in a cheese. The source of milk forming the base of the composition to form the cheese is not important, but may include cow, goat or sheep.

The dietary supplement of the invention can also be added to the whey of goat, cow or sheep milk origin which whey may be obtained during cheese production. The

whey product containing the dietary supplement may be consumed as a drink.

In a further aspect of the present invention, there is provided the use of colostrinin in combination with lactoferrin in the manufacture of a medicament for bringing about an improvement in a individual's immune system.

The dietary supplement of the present invention can result, in adults, in an increase in energy and an apparent increase in clarity of thinking.

The dietary supplement of the invention should preferably not be used for more than 21 days continuously. This is because the phenomenon of tachyphylaxis may otherwise be induced. Tachyphylaxis is the gradual loss of an individual's capability to synthesise cytokines. In this situation an adverse reaction may be experienced. Induction of tachyphylaxis may be avoided by discontinuing the use of the dietary supplement of the invention after 21 days for a period of not less than 3 weeks. Following this brief pause, a new cycle of use can be initiated.

According to another aspect of the present invention there is provided a method of stimulating an individual's immune system, which method consists essentially of administering a dietary supplement of the present invention in unit dosage form, preferably each day for 21 consecutive days.

The invention described above relates to a dietary supplement containing colostrinin and lactoferrin, and to certain uses thereof. In another aspect the invention relates to a dietary supplement comprising colostrinin and selenium; this dietary supplement may be used in the same way as the dietary supplement described above, and may have the same additional components. In yet another aspect the invention relates to a dietary supplement comprising colostrinin and at least one of the cytokines listed above; this dietary supplement may be used in the same way as the dietary supplement described above, and may have the same additional components.

In order that the invention may be more fully understood, the following Examples are given by way of illustration only.

Example 1

Lozenge Formulation

The composition of a lozenge formulation of an example of the dietary

supplement of the invention per unit dose is as follows:

Ingredient	Amount
Sucrose, lactose or trehalose and/or	25 mg
Cold-water-soluble starch	42 mg
Phosphate Buffered Saline	(if required)
Natural colostrinin	100 μg
Selenium (metalloprotein) or other seleno-cysteine-containing proteins	5 μg
Purified recombinant human lactoferrin	10 mg

In all these examples, the colostrinin can be obtained by processes well known in the art. Such processes are described, for example, in the references discussed above. The other materials are also readily available.

Example 2

Method of manufacture of lozenge formulation

A starch gel-based lozenge containing colostrinin, lactoferrin and selenium is prepared by combining 150 g sucrose, 550 ml phosphate 0.15 mm buffered saline, and 250 g of cold-water-soluble starch such as that described in U.S. Patent 4,465,702, heating the mixture with stirring to a temperature of 75°C, cooling the mixture to 30°C and thereafter blending into the paste-like mass with 50 ml PBS containing 3 mg purified human colostrinin, 4.5 mg selenium (rich protein) and 300 mg purified recombinant human lactoferrin. The mixture is then formed into multiple portions of 5 to 10 grams each, which set upon standing under drying conditions to a starch candy gel-like consistency. The lozenges thereby produced can be administered to a patient singly or in combination. The patient is instructed to hold the lozenge in his mouth until it is completely dissolved to release the components for contact with the oral mucosa.

Example 3

Powdered Milk Formulation

A formulation for feeding to a baby post weaning from mother's milk, is:

Proprietary milk powder (e.g. Sma™, White™ by Sma Nutrition, Maidenhead, U.K. *)	4g **
Natural ovine colostrinin	150µg
Selenium (bound to lactobacillus acidophilus)	8.25µg (free selenium)
Human Recombinant Lactoferrin	1.0 mg

* Sma™ ingredients quoted as lactose, skimmed milk powder, vegetable oils, emulsifier (soya lecithin), potassium bicarbonate, vitamin C, taurine, ferrous sulphate, zinc sulphate, cytidine-5'-monophosphate, disodium uridine-5'-monophosphate, vitamin E, adenosine-5'-monophosphate, niacin, disodium inosine-5'-monophosphate, disodium guanosine-5'-monophosphate, pantothenic acid, vitamin A, copper sulphate, thiamin, vitamin B, riboflavin, beta-carotene, manganese sulphate, folic acid, vitamin K, potassium iodide, biotin, vitamin D, vitamin B. Although the manufacturer lists ferrous sulphate as an ingredient, we prefer not to include this material or any other iron containing compounds.

** Follow manufacturer's instructions for dosage guide e.g. weight 6.5 kg, approximate age of baby 4 months, 7 level scoops in 200 ml cooled (freshly boiled) water.

Example 4

Baby Food Formulas

The following formulations may be used for very young babies:

Formulas for new born 1 - 7 days old:

Natural Colostrinin (antibody - colostrinin complex)	50 µg per serving.
Lactoferrin	100 µg per serving.

(human recombinant or natural bovine)

Formulas for 8-14 days old babies:

Natural colostrinin	5.0 µg per serving.
Lactoferrin	100 µg per serving.
Selenium in form of seleno-cysteine	1.0 µg per serving.

Formulas for 15-30 days old babies.

Natural colostrinin	None
Lactoferrin	50 µg per serving.
Selenium	0.5 µg per serving.

Formulas for 31-45 days old babies.

Natural colostrinin complex	10 µg per serving.
Lactoferrin	50 µg per serving.
Selenium	0.5 µg per serving.

It will be appreciated that modifications may be made to the invention described above.

CLAIMS

1. A dietary supplement comprising colostrinin in combination with lactoferrin.

2. A dietary supplement according to claim 1, further comprising selenium.

3. A dietary supplement according to claim 1, wherein the selenium is in the form of a physiologically acceptable selenoprotein.

4. A dietary supplement according to claim 1, further comprising at least one cytokine selected from interferon α, interferon γ, interleukin 1-α, interleukin 1-3, interleukin 6, 8, 10, 12, 16, tissue necrosis factor α, G-CSF, M-CSF, TGFα and TGFβ.

5. A dietary supplement comprising colostrinin in combination with selenium.

6. A dietary supplement comprising colostrinin in combination with at least one cytokine selected from interferon α, interferon γ, interleukin 1-α, interleukin 1-3, interleukin 6, 8, 10, 12, 16, tissue necrosis factor α, G-CSF, M-CSF, TGFα and TGFβ.

7. A baby food formula comprising a dietary supplement according to any preceding claim.

8. The use of dietary supplement according to any preceding claim in a baby food formula.

9. A tablet, lozenge or other solid oral dosage form comprising 12.5 micrograms to 200 micrograms colostrinin, 10 micrograms to 100 milligrams lactoferrin, and 2.5 to 100 micrograms seleno-cysteine in combination with a physiologically acceptable carrier.

10. The use of colostrinin in combination with lactoferrin in the manufacture of a medicament for improving the immune system of mammals.

11. The use of colostrinin in combination with selenium in the manufacture of a medicament for improving the immune system of mammals.

12. The use of colostrinin in combination with at least one cytokine selected from interferon α, interferon γ, interleukin 1-α, interleukin 1-3, interleukin 6, 8, 10, 12, 16, tissue necrosis factor α, G-CSF, M-CSF, TGFα and TGFβ in the manufacture of a medicament for improving the immune system of mammals.

13. A method of stimulating the immune system of a mammal, comprising administering a dietary supplement according to any one of claims 1 to 6 in unit dosage form.

14. A method according to claim 13, wherein the unit dosage form comprises 12.5 micrograms to 200 micrograms colostrinin, 10 micrograms to 100 milligrams lactoferrin, and 2.5 to 100 micrograms seleno-cysteine in combination with a physiologically acceptable carrier.

15. A method according to claim 13 or 14, wherein one unit dose of the dietary supplement is administered each day for a first period of not more than three weeks, then no dosage is administered for a subsequent period of up to three weeks.

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(54) Title: DIETARY SUPPLEMENT CONTAINING COLOSTRININ

(57) Abstract

A dietary supplement comprises a combination of colostrinin and at least one of lactoferrin, selenium or a cytokine selected from interferon α, interferon γ, interleukin 1 - α, interleukin 1 - 3, interleukin 6, 8, 10, 12, 16, tissue necrosis factor α, G-CSF, M-CSF, TGF α and TGF β for promoting the functioning of the immune system.

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 289 278 A (IMMUNO DYNAMICS INC) 15 November 1995 (1995-11-15) page 4, last paragraph -page 5, last paragraph ---	1-15
X	WO 97 43905 A (ADLER CHARLOTTE ;ACHENBACH MICHAEL (DE)) 27 November 1997 (1997-11-27)	1-15
Y	page 2, line 29 - line 35 page 5, line 1 - line 6 page 7, line 12 - line 33 ---	1-15
X	WO 97 05884 A (NEW ENGLAND MEDICAL CENTER INC) 20 February 1997 (1997-02-20) page 3, line 7 - line 25 ---	1-15
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2000	03. 07. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bendl, E

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 015, no. 027 (C-0797), 22 January 1991 (1991-01-22) & JP 02 265458 A (NIKKEN FOOD KK), 30 October 1990 (1990-10-30)	1-15
Y	abstract	1-15
X	WO 98 14473 A (GEORGIADES BIOTECH LTD ;JANUSZ MARIN (PL); LISOWSKI JOZEF (PL); DU) 9 April 1998 (1998-04-09) cited in the application page 3 -page 4	1-15
Y	A.D. INGLOT ET AL.: "Colostrinine: a Proline-Rich Polypeptide from Ovine Colostrum Is a Modest Cytokine Inducer in Human Leukocytes" ARCHIVUM IMMUNOLOGIAE ET THERAPIAE EXPERIMENTALIS, vol. 44, - 1996 pages 215-224, XP000205580 cited in the application left-hand column	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 99/01878

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2289278 A	15-11-1995	US 5645834 A	08-07-1997
		CA 2148963 A	10-11-1995
		IE 950335 A	29-11-1995
WO 9743905 A	27-11-1997	DE 19619990 A	20-11-1997
		AU 3024197 A	09-12-1997
		DE 29623125 U	06-11-1997
		EP 0918464 A	02-06-1999
WO 9705884 A	20-02-1997	AU 6641896 A	05-03-1997
JP 02265458 A	30-10-1990	NONE	
WO 9814473 A	09-04-1998	PL 316416 A	14-04-1998
		AU 4565197 A	24-04-1998
		BR 9712259 A	25-01-2000
		CN 1238782 A	15-12-1999
		EP 0932623 A	04-08-1999
		GB 2333453 A	28-07-1999
		PL 332632 A	27-09-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PAC/19184		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01878	15/06/1999	16/06/1998
International Patent Classification (IPC) or national classification and IPC A23L1/00		
Applicant REGEN BIOTECH LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/01/2000	20.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bendl, E Telephone No. +49 89 2399 8637

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01878

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-9 as originally filed

Claims, No.:

1-15 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10-15 (for industrial applicability).

because:

☒ the said international application, or the said claims Nos. 10-15 (for industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Chapter III ----------

Claims 10 - 15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Chapter V ----------

The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 = GB-A-2 289 278
D2 = WO-A-9743905
D3 = WO-A-9705884
D4 = JP-A-2265458
D5 = WO-A-9814473
D6 = Archivum Immunologiae et Therapiae Experimentalis 44 215-224 (1996)

Novelty

1.) The subject - matter of Claims 1-9 on file does not meet the requirements for novelty (Article 33(2) PCT), because such compositions or their use have already been described in the prior art disclosures.

2.) Naturally occurring colostrum contains the compound colostrinin as well as lactoferrin, cytokines and selenium. Although compounds naturally containing the compounds as claimed are intended to be excluded (see page 2, lines 13/14 of the description on file), such a requirement is firstly not reflected by the claims and secondly the subject - matter of independent Claims 1, 5, 6, 7 and 9 relates to compositions. Thus it would not make any difference whether the active ingredients have been naturally or synthetically produced, since they would not be

different. Consequently, such natural products containing the required compounds (like colostrum) are considered to be novelty destroying.

3.) Since it is furthermore known that colostrum is suitable to stimulate the immune system of babies, the subject - matter of Claims 10 - 13 is considered to be anticipated.

4.) Even if the wording of the claims could be amended in such a way that naturally occurring products (as such) were excluded, novelty still would not be given, because D1 teaches about diet supplements which may be in a dried form (e.g. see page 4, last paragraph) which contains all proteins present in colostrum (see page 5, middle of the page) for improving the immune situation in cows.

5.) Decaseinated colostrum containing the proteins and compounds originally present (for instance TGF-ß - see page 7, lines 26-33; selenium - see page 10) for use in foods and diets, nutrition for babies as well as for improving the immune system (page 7, lines 12-33) have been disclosed in D2.

6.) The combination of colostrum and lactoferrin has been explicitly reported for use in infant formulas in D3 (see page 3).

7.) Combinations of colostrum and selenium for activating the immune system have been reported in D4 (see the abstract).

Inventive step

1.) Even if the requirements for novelty were met, there would not seem to be any inventive step (Article 33(3) PCT). It is known from documents D1 - D4 mentioned above as well as from D5 (cited in the application on file) that colostrum or its proteins including colostrinin are suitable as additive to foods (e.g. to infant formulas) in order to stimulate the immune system. The combination with other immunoactivating substances has been recommended in D4, in D6 (see page 223, left-hand column) it is derivable that the presence of other cytokines may influence the activity. Thus, the uses and the combinations as well as the products

described are considered to be obvious vis-à-vis the available documents of the prior art.

2.) Dependent claims can only be regarded as formally meeting the requirements for novelty and inventive step if they refer to an independent claim which meets these requirements.

Industrial applicability

For the assessment of the present claims 10 - 15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Chapter VIII ----------

1.) Superfluous expressions like the last two lines on page 9 of the description should have been deleted.

2.) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 - D4 are not mentioned in the description, nor are these documents identified therein.

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
PAC/19184		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/ 01878	15/06/1999	16/06/1998
Applicant		
REGEN BIOTECH LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   DIETARY SUPPLEMENT CONTAINING COLOSTRININ

5. With regard to the **abstract**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01878

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A dietary supplement comprises a combination of colostrinin and at least one of lactoferrin, selenium or a cytokine selected from interferon α, interferon γ, interleukin 1 - α, interleukin 1 - 3, interleukin 6, 8, 10, 12, 16, tissue necrosis factor α, G-CSF, M-CSF, TGF α and TGF β for promoting the functioning of the immune system.